REMARKS

Entry of the instant amendment and reconsideration of the above-identified application as amended is respectfully requested.

Claims 6-16, 18-21 and 28-31 were previously presented in the application. Claims 1-5 are withdrawn from consideration.

Claims 8-11, 13-16 and 18-21 have been amended to correct obvious errors in the claim dependencies.

New claim 32 has been added to more adequately claim a particular aspect of the present invention.

Briefly, the present invention provides a method of synergistically enhancing the chemotherapeutic treatment of cancer expressing adenosine A_3 receptors comprising administering to a mammal in need thereof an effective amount of a high affinity adenosine A_3 receptor antagonist of the present invention either prior to or during administration of a chemotherapeutic cancer agent, support for which may be found throughout the specification.

For example, the results shown in Tables 4 to 8, starting on page 23, indicate synergistic enhancement of the growth inhibitory activity (anti-proliferative activity) of a number of chemotherapeutic cancer agents in the presence of an adenosine A_3 receptor antagonist as determined from the measurement of the enhancement factor (for enhancement and enhancement factor please see a paragraph starting on line 25 on page 12, and a section starting on line 20 on page 16). As the results show, synergistic enhancement of the growth inhibitory activity of taxane compounds, e.g., paclitaxel and docetaxel; vinca alkaloids, e.g., vinblastine; camptothecin compounds, e.g., irinotecan; and antibiotics, e.g., doxorubicin; is observed consistently in the presence of an adenosine A_3 receptor antagonist, e.g., MRE3008F20, IL-10 and IL-11, when tested in different cancer cell lines.

The synergistic effects of the combination of the present invention are further established, e.g., by colony formation experiments: the adenosine A_3 receptor antagonist MRE3008F20 (10 μM) and the taxane compound paclitaxel (0.75 ng/ml) each alone decreases colony formation of A375 cells to 59 and 64% of the control, respectively. Surprisingly, when

MRE3008F20 is combined with paclitaxel, virtually all colony formation ceases (please see second, third and fourth paragraphs on page 27).

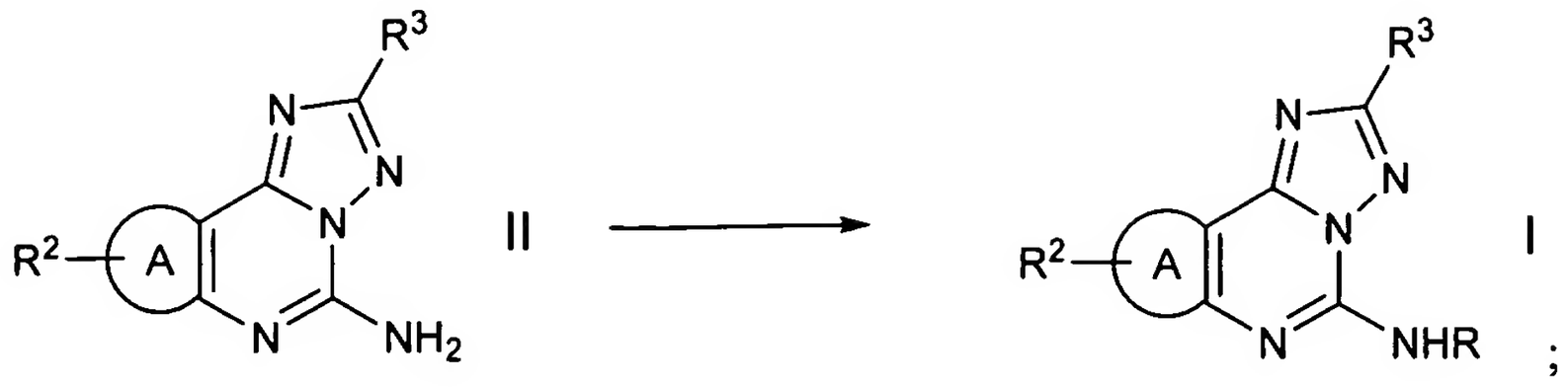
The synergism seen with adenosine A_3 receptor antagonists and chemotherapeutic agents, e.g., taxanes, will allow the use of lower doses of the cytotoxic agent, thus, avoiding toxic effects that are limiting in all cancer treatment paradigm. Adenosine A_3 receptor antagonists by themselves have been found to be relatively non-toxic at doses that produced synergism as described in the present application.

Furthermore, it has now been discovered by the Applicants that adenosine A_3 receptor antagonists, in particular those disclosed in the instant application, are direct inhibitors of P-glycoprotein mediated drug-efflux in several cancer cell lines thereby suppressing multi-drug resistance (MDR) as summarized in the section starting on page 31, last paragraph, and ending on page 33. For example, MRE3008F20 blocks the P-glycoprotein mediated rhodamine 123 (Rh 123) transport in A375 cells completely at 10 μM concentration.

I. Claim Rejection under 35 U.S.C. § 112, First Paragraph

Claims 9 and 20 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In the Examiner's opinion the claims contain subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, i.e., there is no teaching in the instant Application or in the prior art for the making of the claimed compounds wherein A is a triazolo ring.

It is respectfully submitted that one skilled in the art would know how to make compounds of the present invention wherein A is a triazolo ring by following the teachings of WO 00/15231, a copy of which is enclosed herewith. For example, WO 00/15231 discloses how to make adenosine A_3 receptor antagonists of the present invention, i.e., compounds of formula I, shown below, wherein A, R, R^2 and R^3 have the meanings as defined in the instant application (and in WO 00/15231), by reacting a compound of formula II



with a suitable carboxylic acid or sulfonic acid derivative using known chemistry, e.g., as illustrated for compounds (42) to (59) on pages 45-51.

Furthermore, WO 00/15231 teaches how to make compounds of formula II wherein A is a triazolo ring as illustrated in Schemes III through V for compounds wherein R^3 is furan, starting on page 20, and further exemplified in the illustrative Examples 8 and 12-15 starting on page 54 and 61, respectively.

Although, WO 00/15231 does not disclose any specific examples of compounds of formula I wherein A is a triazolo ring, one skilled in the art would know how to make and/or use said compounds without undue experimentation after reading the teachings in WO 00/15231.

In view of the above, it is respectfully submitted that the rejection under 35 U.S.C. § 112, first paragraph, is unwarranted and should be withdrawn.

II. Claim Rejection under 35 U.S.C. § 103(a)

Claims 6-8, 10-16, 18-19, 21 and 28-31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,210,917 to Carson et al. in view of U.S. Patent No. 6,066,642 to Jacobson et al. and further in view of Baraldi et al. "Pyrozolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine derivatives as highly potent and selective human A_3 adenosine receptor antagonists", Journal of Medicinal Chemistry *42*, 4473-4478 (1999).

1) *Carson et al.* teaches a combination therapy comprising an adenosine-5'-triphosphate (ATP) depleting agent to treat cancers such as breast and colon cancer that are multi-drug resistant (MDR) with respect to vinca alkaloids, taxanes and antibiotics. Carson et al. additionally explains that the depletion of adenosine-5'-monophosphate (AMP) and ATP negatively effects P-glycoprotein activity thereby suppressing MDR.

Carson et al. does not suggest that adenosine A_3 receptor antagonists could be employed to inhibit P-glycoprotein activity in tumor cells thereby suppressing MDR.

As to the Examiner's opinion that Carson et al. teaches that depletion of adenosine is linked to P-glycoprotein dependent MDR, it is respectfully submitted that Carson et al. explains how P-glycoprotein, an energy dependent drug-efflux pump, may be blocked by mechanisms that decrease cellular energy sources, namely AMP, ADP and ATP, not adenosine, thereby rendering P-glycoprotein inactive and reducing MDR. In the contrary, as described in the instant application, adenosine A_3 receptor antagonists, in particular those disclosed in the instant application, are direct inhibitors of P-glycoprotein activity thereby suppressing MDR. Adenosine A_3 receptor antagonists do not reduce AMP, ADP or ATP levels.

2) *Jacobson et al.* teaches the use of adenosine A_3 receptor antagonists in the killing of cancer cells (Example 31, column 63) wherein the A_3 receptor antagonists may be used alone or in combination with other pharmaceutically active compounds.

Jacobson et al. does not disclose or suggest the combination treatment of the present invention. Although, Jacobson et al. discloses a general statement regarding combinations, the reference does not disclose any potential combination partners, or uses thereof, in particular not the chemotherapeutic treatment of cancer by employing the combinations of the present invention.

As to the use of adenosine A_3 receptor antagonists in the killing of cancer cells, it is respectfully submitted that Example 31, although exploring cell death in the presence of adenosine A_3 receptor antagonists, does not show clear evidence whether adenosine A_3 receptor agonists or antagonists should be used in the treatment of diseases such as cancer. For example, in accordance with Example 31, last paragraph (column 66), cellular protection as well as programmed cell death can be mediated by both agonists and antagonists, and the level of agonist and antagonist should be carefully balanced to obtain the desired effect on the cells, e.g., death or protection.

Clearly, Jacobson et al. does not provide motivation or reasonable expectation of success for one skilled in the art to employ combinations of the present invention for the chemotherapeutic treatment of cancer.

3) *Baraldi et al.* teaches that MRE3008F20 is an adenosine A_3 receptor antagonist.

Baraldi et al. does not describe or suggest the combination treatment of the present invention.

As to the Examiner's opinion that all three references teach that reduction in adenosine levels would be efficacious in the treatment of cancer, it is respectfully submitted that no such disclosure may be found in any of the references. In the contrary, it is known in the art that adenosine A_3 receptor antagonists do not reduce adenosine levels.

In view of the above, there is nothing in Carson et al., Jacobson et al. and Baraldi et al. alone or combined that would suggest or motivate one skilled in the art to combine an adenosine A_3 receptor antagonist with a chemotherapeutic cancer agent to achieve a synergistic enhancement in the chemotherapeutic treatment of cancer by employing such a combination, as is now demonstrated by the present invention.

Accordingly, reconsideration of the rejection of claims 6-8, 10-16, 18-19, 21 and 28-31 under 35 U.S.C. § 103(a) is respectfully requested.

III. Claim Rejection under Judicially Created Doctrine of Obviousness Type Double Patenting

In response to the obviousness type double patenting rejection of instant claims 6-16, 18-21 and 28-31 over claims 1-27 of co-pending application No. 10/600,116, filed June 20, 2003, Applicants are enclosing herewith a Terminal Disclaimer under 37 C.F.R. § 1.321.

IV. Conclusion

It is respectfully submitted that the subject matter of the instant claims is fully supported by the enabling disclosure of the instant application, and no new subject matter has been incorporated by the above amendments.

In view of the foregoing, the instant application is believed to be in condition for allowance and such is earnestly solicited.

Respectfully submitted,

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